

# Newer Laboratory Approaches for Assessing Visual Dysfunction

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The crucial point that will be emphasized throughout this report is the potential utility of analyzing visual cortical receptive field (RF) properties at the single-cell level as a sensitive and reliable neurotoxicity screening tool. Numerous studies employing exposure of kittens to altered visual environments during the critical period have demonstrated that particular classes of RFs can be selectively affected while sparing others. There has been a rapid proliferation of new methods used to investigate such effects. An important current trend involves the development of multidisciplinary combinations of approaches. The various maneuvers reviewed here seem adaptable to studying neurotoxic insult of the sensitive properties of cortical visual neurons, particularly in the cat or monkey. Conceivably, a general disruption of cortical RF properties might be expected following toxic exposure since individual RF properties are generally not determined by completely independent mechanisms. In fact, some toxicants might produce a general degradation of RF properties akin to the electrophysiological results reported for long-term dark rearing or binocular deprivation.

## Visual Cortical Receptive Fields and Their Properties

Over the past 20 years, a number of basic concepts have emerged concerning the organization of the mammalian visual system, particularly at the cellular level. A centrally important concept, which ultimately describes the fundamental building blocks of visual circuitry, is the receptive field (RF). Each neuron along the retino-geniculo-cortical pathway (as well as other visual pathways) is concerned with the analysis of a small subregion of the total visual field. At each level, the RFs are arranged in a systematic topographic (i.e., retinotopic) manner such that the entire visual world is laid out multiply across the occipital cortex with an overrepresentation of the central region. A specific stimulus presented within the boundaries of a cell's RF will evoke a maximal discharge of impulses from that cell. The particular stimulus pattern evoking the strongest

response is said to embody the "stimulus trigger features" or RF properties of that cell. For example, a well-known stimulus requirement of cortical units is orientation or angular position of the "best" or optimal stimulus.

Although there is a significant literature on primates, most of our knowledge of how RF properties code form, movement, and depth in the visual world has been obtained from the feline visual system by using recently developed micro-electrode recording and stimulating techniques. The domestic cat has been so widely used as a subject that its use in the vision laboratory has been characterized as "... currently representing the primary source of neural building blocks from which the majority of models of human vision are constructed . . ." (1). In a series of pioneering studies on the feline visual system, Hubel and Wiesel (2, 3) laid down the basic foundation for interpreting the specific RF properties of cortical visual neurons.

The two RF properties that have received the most attention are ocular dominance and orientation selectivity. In the normal mammalian visual cortex, the majority (80-85%) of cortical neurons

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receive excitatory input from each eye, i.e., they are binocular. The remaining small population of cells, categorized as monocular units, receive input from one eye or the other. Furthermore, for cells receiving a dual input, that input is not necessarily equal for the two eyes. A seven-class scheme or an ocular dominance (OD) index characterizing this relative ocular input to a particular cortical cell was proposed by Hubel and Wiesel (2). This nomenclature has been universally adopted among visual neurophysiologists, and probably represents the easiest RF property to determine. A typical OD histogram and definitions for the various categories appear in Figure 1. For a normal adult cat, the distribution for a population of cortical cells is bell-shaped with some contralateral skewing.

Of all the specific stimulus trigger features of visual cortical RFs, perhaps the most fundamental requirement is orientation specificity. That is, the appropriate stimulus must assume some critical angular position within the boundary of the RF for maximal stimulation of that cortical unit, and any deviation ( $\pm 10$ - $25^\circ$ ) from the optimal orientation results in dramatically decreasing or eliminating the neural response. Typically, angular selectivity is determined by moving an appropriate stimulus, usually a light or dark edge (e.g., a bar), through the RF at different orientations while measuring

the response. The response profile of a single cortical cell as a function of stimulus orientation is referred to as the orientation tuning curve (OTC), depicted in Figure 2 for an hypothesized RF. An OTC can be compiled by one of two RF plotting techniques. The first consists of simply listening to the amplified response of the unit over an audio monitor while simultaneously monitoring the activity on an oscilloscope (the manual/auditory feedback method popularized by Hubel and Wiesel) (2, 3). The second approach, one advantage of which is to eliminate possible experimental bias, uses a computer or automatically controlled visual stimulation system. Measurements of orientation preference and the degree of selectivity made by these two methods generally stand in good agreement with each other (4).

There exists an elegant layout of ocular dominance and orientation specificity within the cortex which has been convincingly demonstrated electrophysiologically and anatomically in both the cat and monkey striate cortex (5-8). Two independent sets of vertical "columns" or cortical slabs, ocular dominance and orientation, represent the fundamental building blocks of visual cytoarchitectonics. Cells favoring the same eye or preferring approximately the same optimal stimulus orientation are grouped into functional slabs arranged perpendicularly to each other and the cortical surface and through the six layers of gray matter reveal systematic changes in both ocular dominance and orientation preference. Orientation changes occur in a clockwise or counterclockwise direction such that  $180^\circ$  is represented across about 1 mm of cortex before a reversal. All orientations are about equally repre-

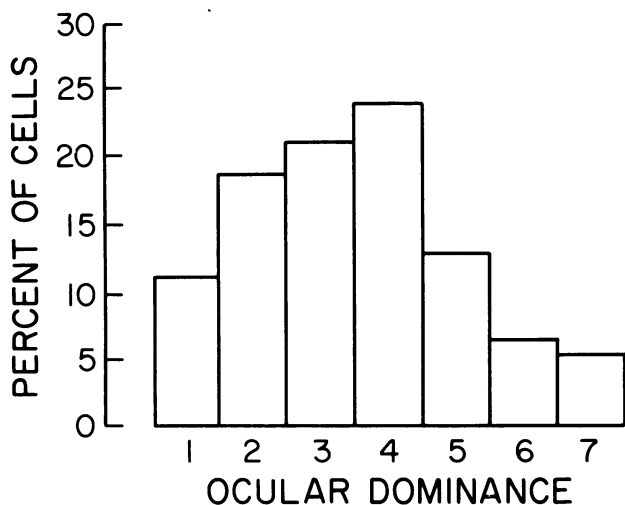


FIGURE 1. Ocular dominance histogram showing the relative influence of the two eyes on a sample of cortical units in a normal adult cat. Each cell is assigned to one of seven categories: Monocular cells are driven exclusively by the contralateral eye (1) or the ipsilateral eye (7), while binocular cells are driven equally by each eye (4), more strongly by the contralateral eye (2 or 3), or more strongly by the ipsilateral eye (5, 6).

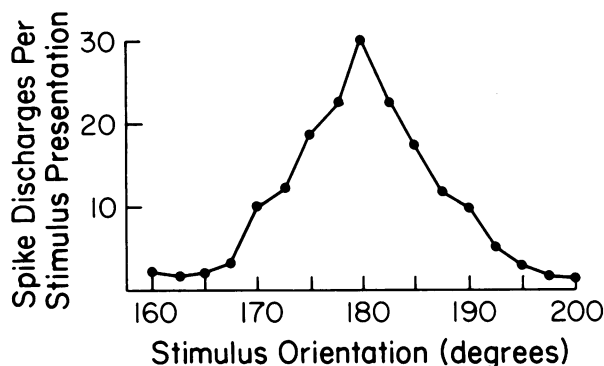


FIGURE 2. Computer determined orientation tuning curve for a cortical cell's receptive field, showing the response to a slit of light at several orientations. This cell is tightly tuned for a stimulus oriented near  $180^\circ$ .

sented with neighboring columns varying by about 10-15°. Likewise, ocular dominance changes progressively; one eye is dominant, then the two become roughly equal, and finally the other eye becomes dominant in roughly the same cortical distance but independently of a 180° orientation sequence. One complete set of these columns, an orientation cycle or ocular dominance cycle, has been termed a hypercolumn.

Another RF feature characteristic of most normal cortical neurons is that a more vigorous response is elicited by a moving than a stationary stimulus. Furthermore, the majority of cortical units display a directional preference, responding more strongly to movement of the optimal stimulus in one direction than in the other direction. This is illustrated in Figure 3; the cell prefers the appropriate stimulus moving in a downward direction orthogonal to the optimal orientation. Other RF properties of cortical visual neurons include the spatial layout of excitatory and inhibitory subregions (shape) which compose a RF, preference for specific velocities of a moving stimulus, and interocular relationships such as RF locational or orientational disparities of binocular cells.

Based on the uniformity in RF properties, cortical units have been categorized by various investigators. The most commonly used system comes from the early studies of Hubel and Wiesel (2, 3) who proposed the now classic simple, complex, and hypercomplex RF types. Extraction of stimulus features from the visual world, as conceived by these authors, is carried out by a hierarchical arrangement of these three basic RF types in visual cortex. In this model the properties of simple cells' RFs are determined by direct excitatory input from

a number of lateral geniculate cells, while the RFs of complex cells are determined by input from several simple cells. Complex cells, in turn, provide the input to the RFs of hypercomplex cells. This strictly serial model, however, has been seriously challenged on both anatomical and electrophysiological grounds (9). The central visual circuitry, particularly from retina to cortex via the dorsal lateral geniculate nucleus, comprises several functionally distinct, parallel-running subgroups of cells, two of which have been called the *X*- and *Y*-pathways. At the cortex, these separate systems are less easily identified, although several electrophysiological studies point to a strong correlation between particular RF types and these parallel afferents. It is currently thought that the *X*-system influences mainly simple cells while the *Y*-system influences mainly complex cells. Important clues to understanding the functional roles of the *X/Y* dichotomy have been provided by differences in retinal distribution, spatial and temporal stimulus properties defined electrophysiologically, and cortical synaptology. The *X*-system is primarily concerned with detailed, central vision and binocular stereoscopic vision, while the *Y*-system subserves some functions of peripheral vision, such as the detection of motion, location, and possibly coarse outlines.

## Neuroelectric Approaches

Generally, more varied and advanced methods of assessment exist for the visual system than for other sensory systems. Like all sensory systems, its development is susceptible to environmental factors, including chemical agents; i.e., although genetics defines the potential, a high level of neuronal plasticity is present. Postnatal plasticity is greatest during early development, a time referred to as the critical period (CP), since normal visual experience during this time is crucial to normal development: Absences or abnormalities in visual experience are manifested as long-lasting functional and physiological deficits. For example, occluding one eye (monocular deprivation or MD) of a kitten during the traditionally defined CP, 1-4 months of age, results in a loss of vision through that eye and a severe shift in ocular dominance in favor of the experienced eye (10). It is of particular interest to visual scientists to determine the extent to which RF properties as well as overall visual physiology are influenced by innate factors, passive maturational changes, and environmental contributions. That is, at each developmental stage, to what extent is the system susceptible to impairment or loss of function due to various degrees of abnormal experience?

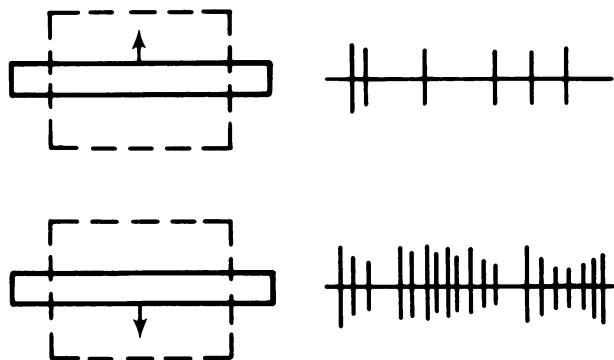


FIGURE 3. Schematic representation of directional selectivity for the same unit as in Fig. 2. Shown on the left is a slit of light moving through the receptive field in both directions, orthogonal to the optimal orientation. On the right are responses evoked by these stimuli.

Since alterations in neural function following exposure to toxic substances, especially at long-term low-level exposures, are often quite subtle, and because it is necessary to determine threshold levels for toxins, it is desirable to have measures of nervous system function which are very sensitive. One suitable tool may be the neurophysiological method of single-cell recordings. RF properties of single cells are finely tuned, and are highly sensitive and responsive to environmental manipulations during the CP. In particular, the properties of ocular dominance, orientation preference, and directional preference have demonstrated highly robust effects. For example, a number of innovative studies (11, 12) have found that if only one orientation (e.g., vertical) is experienced during the CP, most cortical cells will be tuned to that orientation.

In most of these "environmental surgery" studies, animals have been exposed to a unique visual experience throughout the CP. However, some researchers, with the goal of determining the sensitivity of the system, have attempted to delineate the minimal amount of experience needed to alter RF properties. One interesting, but controversial, study (13) reported that as little as 1 hr of exposure to a highly redundant environment (vertical gratings) could significantly alter the normal orientation distribution in kitten cortex, i.e., disproportionately many cortical units were tuned to vertical orientations. Others have shown that ocular dominance can be dramatically shifted following only a few hours of monocular exposure during the peak of the CP (14). On the other hand, important differences in the degree of susceptibility of certain RF properties to environmental insult are beginning to be unraveled. Velocity preferences, for example, appear to be more resistant to a "matching effect" than any other RF property (15). Others contend that certain subclasses of orientation preference are also quite resistant to environmental manipulations, pointing to a strong genetic determination (16). In short, this sort of selective versus instructive question currently represents a major controversy among visual neurophysiologists. Since exposure to toxic substances can be restricted to either prenatal or postnatal periods, or be of a more chronic nature throughout adult life, knowledge of such developmental differences and their chronologies provides still another means for measuring the relative sensitivity of the visual system to neurotoxicity at the level of individual RF properties.

The effect of chemical agents on RF properties is a topic which has scarcely been broached, but indications are that this might be a highly sensitive and responsive measure, useful for revealing mechanisms of dysfunction. For instance, two observa-

tions made on cats during acute single unit preparations are: administration of barbiturate anesthetic agents leads to a sharpening of orientation tuning of visual cortical units (17) and improper regulation of oxygen, as measured by end-tidal CO<sub>2</sub> concentration, leads to a rapid and severe degradation of visual RF quality, e.g., high erratic base rate and poor responsiveness (18). Another study, explicitly addressing changes in visual RF properties following neurotoxic exposure, reported that the widely used organophosphate pesticide, mevinphos, and related cholinergic drugs (agonists such as pilocarpine or antagonists such as atropine sulfate) abolish the highly tuned directional selectivity of single cells in the avian nucleus rotundus (19). A similar effect was reported following ethanol exposure. These effects may be the neuronal basis for visual behavioral impairment at certain levels of intoxication (decrease or loss of visual attention, orientation behavior, and peripheral vision).

Another neuroelectric technique, one which has already been widely adapted for neurotoxin testing, is the visually evoked potential (VEP) (20). The VEP is a gross recording, obtained through scalp or depth electrodes, which simultaneously measures thousands of cells' responses to visual stimulation. The EP signal is generally localized to the small area of brain directly below the electrodes. Since the response is obscured in a single trace due to trial-to-trial variability, inherent noise, and background EEG, a reliable EP record is obtainable only through signal averaging techniques. A standard cortical VEP (VECP) record evoked from visual cortex by a light flash is diagrammed in Figure 4. Like all EPs, the VECP is a complex waveform consisting of a series of positive (P1, P2, P3) and negative (N1, N2, N3) peaks, the amplitude and latency of which are determined by a number of factors: stimulus parameters, location and mode of recording and age and physiology of the animal. Two phases comprise the VEP, and

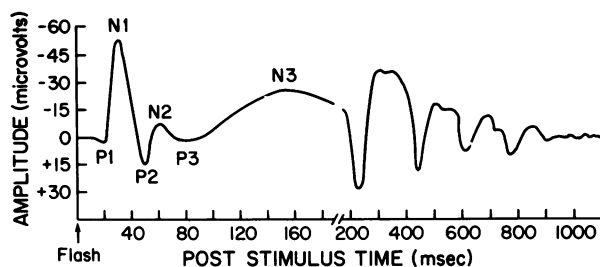


FIGURE 4. Electrical activity in rat visual cortex following a light flash, showing the various components of the evoked potential and the subsequent 3-6 Hz afterdischarge. After Fig. 1 of Dyer et al. (20).

alterations in peak onset latency or amplitude (baseline-to-peak or peak-to-peak) of specific components may reveal CNS dysfunction. The early primary components (latency < 50 msec), P1-N1 and N1-P2 are most sensitive to changed input parameters and are commonly thought to depend upon retino-geniculate activity, while the late secondary components (50-200 msec latency), P2-N2, N2-P3 and P3-N3, which are believed related to diffuse activity of thalamic, mesencephalic, and cortical origins, are quite variable in waking brains and are suppressed by anesthetics.

This technique has several advantages over single-unit records: (1) it can be quickly, easily, and repeatedly applied, and (2) it can be applied to humans as well as animal subjects. Its use as a research tool for determining mechanism of dysfunction, however, is restricted to a molar level. Clearly, it is of considerable theoretical and practical importance to establish correlations between specific parameters of gross evoked potentials, on the one hand, and the activity of various classes of single units on the other hand. A number of studies have approached this question (21), but a comprehensive picture has not yet emerged.

The ease with which the VEP can be measured has made it a prime candidate for clinical use, epidemiological or experimental field studies, and longitudinal studies. It is currently used as a diagnostic tool for amblyopia in very young children and other nonverbal patients. Also, it has been proposed for use in evaluating neurotoxicity in individuals who have had prolonged occupational contact with possibly toxic substances. However, little toxicological information is actually obtained from human subjects since controlled administration of toxins cannot exceed threshold levels. For developmental or longitudinal studies, the VEP is well-suited since components emerge in a chronologically orderly sequence and the waveform, which does not assume adult characteristics until a relatively late developmental stage, changes again during senescence (22).

The VEP is currently being used to study effects of such common toxicants as CO, some heavy metals (lead, methylmercury), and some organophosphate compounds (mevinphos). For example, one study of the effects of methylmercury (23) reported that rats prenatally exposed to this heavy metal (their mothers ingested a single low dose) showed a visual dysfunction, as measured by the VEP, in adulthood. The early primary VEP components in these animals had an increased amplitude, relative to controls, indicating a disruption of function in the retinogeniculate-striate system. Also, the P2 and N2 peaks had a shortened

latency, which in conjunction with other reports, suggests a greater susceptibility to damage by methylmercury for slowly conducting axons than for other axons.

A common feature of mammalian visually evoked cortical activity which follows the VEP (120-200 msec latency) and persists for 2 sec or longer is a rhythmic 3-6 Hz repetitive discharge known as the visually evoked response afterdischarge (VER AD) (Figure 3). It is generated and maintained by recurrent circuitry at the dorsal LGN level and is modulated by a variety of limbic, brain stem, and thalamic systems (24, 25). This response, which has only recently been explored, is a sensitive measure of visual dysfunction caused by some substances when the VEP is insensitive. The VER AD is especially sensitive to drugs such as convulsants and anticonvulsants having a predominantly thalamic level of action. Thus one promising use of the VER AD is as a model for the treatment of epilepsy.

## Neurochemical Approaches

Studies of chemically induced changes in single visual cortical neurons are quite limited, although the development of new neurochemical techniques has made this a major objective. Potentially fruitful approaches for assessing the effects of both acute and chronic administration of toxic substances to developing and adult visual cortical neurons have been provided by studies of specific functions of neurotransmitters in visual cortex. The value of this technology is that it permits relatively specific pharmacological control of locally applied chemicals to sensory regions (e.g., visual cortex) of the brain and concurrent or subsequent electrophysiological evaluation of specific, patterned cellular activity evoked by appropriate sensory stimuli. In particular, two techniques have been used in elucidating neurochemical mechanisms operating in the visual cortex of the cat. Importantly, both allow for within-animal controls, such as interhemispheric comparisons.

The first preparation, most suited to ascertain immediate or acute effects of exposure to toxic substances, is the microiontophoretic administration of substances of interest while simultaneously recording single-cell activity. Briefly, this technique involves penetrating the visual cortex with multibarrel micropipets. Typically, the center barrel is used as a recording/marketing electrode for single units while the other barrels contain agents to be released at specific sites by passing a small ejecting current through the desired solution. For example, Sillito (26) and others (27) have demon-

strated in visual cortex that the action of  $\gamma$ -aminobutyric acid (GABA), an important inhibitory neurotransmitter in the mammalian brain, can be reversibly antagonized by iontophoretic application of the alkaloid, bicuculline. The general effect of bicuculline on single cells is a disruption of response specificity for stimulus parameters such as orientation and direction of movement. In addition to the general disruption of RF properties, specific differences were noted for RF types such as simple versus complex. A corollary question, arising from these specific cortical effects following neurochemical manipulations, is: To what extent are specific differences manifested systematically throughout the central visual pathways following environmental insult, such as from toxic exposure, since functionally different systems (e.g., the X/Y dichotomy) are believed to be connected to these different cell types? Such an assessment would offer a means for measuring the relative sensitivity of the visual system to neurotoxicity at a more integrative level. The primary impetus for investigating these functional differences has already been provided by studies which have demonstrated that special critical period exposure for kittens can selectively disrupt normal function of the Y-system, while the same maneuver, in this case paralysis of one eye, performed on the adult cat degrades the X-system (28).

Equally important questions concern changes in visual cortical RF properties following chronic administration of chemical agents, or low-level exposures during early postnatal development. Consequences in the latter case may not be fully manifested until late in life and may thus demand longitudinal analysis. A preparation, quite adaptable for these maneuvers, involves a continuous microperfusion technique using the newly developed Alzet osmotic minipump. Like the first technique, it, too, has yielded a means for coupling neurochemical and electrophysiological approaches in the study of single neurons in the developing and adult visual cortices. This simple procedure involves subcutaneously implanting a minipump system with a connecting cannula that delivers the contents slowly and continuously over a specific cortical site. After the contents have been emptied, minipump replacement, if so desired, can be performed easily and quickly. Subsequently, electrophysiological examination of single neurons is performed, using conventional procedures. Most recently, this preparation has been employed to investigate neurochemical mechanisms that possibly control the time course of the postnatal CP as manifested by the monocular deprivation effect in the feline visual system. Intraventricular injections (29) or local cortical

microperfusions via an implanted osmotic minipump/cannula system (30) of the neurotoxin, 6-hydroxydopamine (6-OHDA), prevent the loss of binocularity which normally follows monocular deprivation during the CP. These findings, along with subsequent studies, indicate that a normal balance of catecholamines plays a crucial role in promoting neuronal plasticity in the feline visual system. For example, concurrent microperfusion of the visual cortex with 1-norepinephrine HCl blocked the 6-OHDA effect for monocularly deprived kittens, who then showed the expected shift in ocular dominance (31). Furthermore, the susceptibility to monocular deprivation of kittens well beyond the CP (13 weeks) and, to a lesser degree, adult cats (2 years old) is restored by extended periods (2 weeks) of cortical microperfusion with norepinephrine (30).

## Behavioral Approaches

Behavior is the most complex but also the most relevant level at which the effects of environmental manipulations can be examined. The assessment of visual behaviors, which has been extensive in the cat, has been approached in various ways. The first has involved observing and cataloguing naturally occurring visual behaviors in the normal adult organism. A second approach, related to the first, entails evaluating the development of such behaviors and various factors that affect them, especially during development. Commonly studied visual behaviors have traditionally included gross visuo-motor responses such as the looming reflex, visual orienting, following and pursuit of visual targets, obstacle avoidance in an open field, triggered visual placing, coordinated jumping, and depth perception as tested on a visual cliff. Unfortunately, a good correspondence between visual deficits defined physiologically at the single-cell level and behaviorally via gross visuo-motor performance may not occur. These behavioral tests are often not sensitive enough, and further, extensive visuo-motor adaptation can mask real deficits or anomalies of visual function. Tests using refined and controlled psychophysical procedures have provided the necessary sensitive measures of visual function in normal and experimental animals. Attention will be confined to these procedures since they offer a method for pinpointing the nature and chronology of sensory deficits and, more importantly, a means for comparison of human and infrahuman results.

Two behavioral tests, a nose-key operant (4, 32) and a modified Lashley jumping stand (33) require an animal to perform in a two-response forced-choice discrimination task. These tests have con-

siderable appeal since training is relatively fast and easy, allowing a variety of visual functions with known parameters for humans to be determined: acuity, orientation perception, depth perception, vernier alignment, and contrast sensitivity. With these techniques the functional significance of single-unit disruption can be directly addressed; i.e., does the quality of RF properties define visual capacities? Several studies have provided partial answers: A kitten monocularly deprived during the critical period has a mostly monocular cortex, as seen by single-unit studies (10). The behavioral manifestation, determined using a conditioned suppression paradigm, is that binocular visual functions (e.g., stereopsis) are absent or extremely attenuated (34). A second manipulation, which alters the cortical distribution of RF orientations, has been shown to affect perceptual performance as well. Kittens reared experiencing a restricted range of orientations (horizontal or vertical) develop biased visual cortices (i.e., most units are tuned to horizontal and vertical, respectively) and are visually more sensitive to the experienced orientations (4).

## Conclusions

The relative sensitivity of visual cortical RF properties to environmental influences suggests a potential utility of RF analysis as a neurotoxicity screening tool. New and improved laboratory techniques including neuroelectric, neurochemical, and behavioral approaches adaptable to this area of research were briefly reviewed. Their usefulness as screening tools remains to be fully demonstrated.

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